

MARKED UP COPY OF AMENDMENT

--10. (Twice amended) A method for the prophylactic and/or therapeutic treatment of dysuria that comprises:

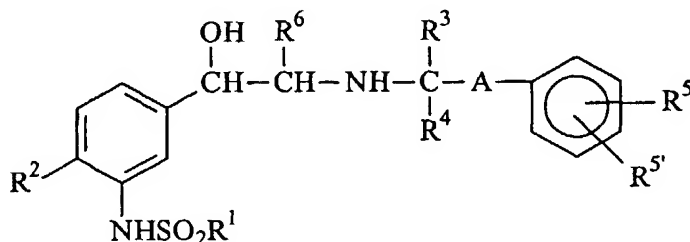
administering to a human being or an animal an effective amount of a compound, which is a β_3 adrenergic receptor agonist, having a general formula selected from the group consisting of formula (IV), (V), (VI), (VII) and (VIII),

or a salt or prodrug thereof, or for the compound of formula (VII) an ester or amide thereof;

wherein

(a) a compound of formula (IV) is represented by the following general formula:

wherein

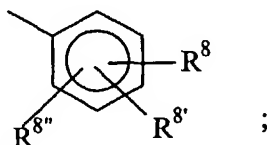


(IV)

R^1 is lower alkyl, aryl or [arylalkyl] arylalkyl;

R^2 is hydrogen, hydroxy, alkoxy, $-CH_2OH$, cyano, $-C(O)OR^7$, $-CO_2H$, $-CONH_2$, tetrazole, $-CH_2NH_2$ or halogen;

R^3 is hydrogen, alkyl, heterocycle or



R^4 is hydrogen, alkyl or B;

R^5 , $R^{5'}$, R^8 , $R^{8'}$ and $R^{8''}$ are independently hydrogen, alkoxy, lower alkyl, halogen, $-OH$, $-CN$, $-(CH_2)_nNR^6COR^7$, $-CON(R^6)R^{6'}$, $-CON(R^6)OR^{6'}$, $-CO_2R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$,

$-N(R^6)SO_2R^1$, $-N(R^6)R^6$, $-NR^6COR^7$, $-OCH_2CON(R^6)R^6$, $-OCH_2CO_2R^7$ or aryl; or

R^5 and $R^{5'}$ or R^8 and $R^{8'}$ may together with the carbon atoms to which they are attached form an aryl or heterocycle;

R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; and

R^7 is lower alkyl;

R^9 and $R^{9'}$ are independently hydrogen, lower alkyl, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; or

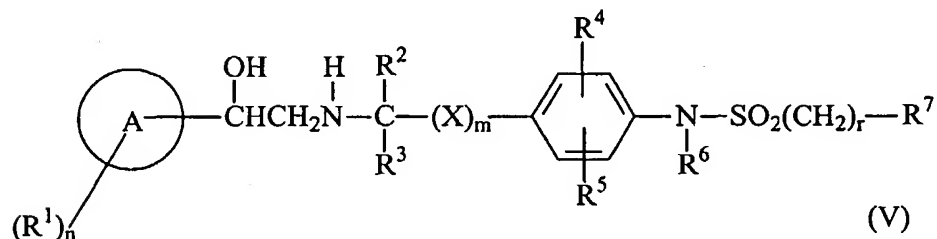
R^9 and $R^{9'}$ may together with the nitrogen atom to which they are attached form a heterocycle;

A is a bond, $-(CH_2)_n-$ or $-CH(B)-$, wherein n is an integer of 1, 2 or 3 and B is $-CN$, $-CON(R^9)R^{9'}$ or $-CO_2R^7$;

with the proviso that when A is a bond or $-(CH_2)_n-$ and R^3 is hydrogen or unsubstituted alkyl, then R^4 is B or substituted alkyl;

(b) a compound of formula (V) is represented by the following general formula:

wherein



n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is pyridinyl;

R^1 is (1) hydroxy, (2) oxo, (3) halogen, (4) cyano, (5) NR^8R^8 , (6) SR^8 , (7) trifluoromethyl, (8) C_1-C_{10} alkyl, (9) OR^8 , (10) SO_2R^9 , (11) $OCOR^9$, (12) NR^8COR^9 , (13) COR^9 , (14) $NR^8SO_2R^9$, (15) $NR^8CO_2R^8$, or (16) $[C_1-C_{10}]$ C_1-C_{10} alkyl substituted by hydroxy, halogen, cyano, NR^8R^8 , SR^8 , trifluoromethyl, OR^8 , C_3-C_8 cycloalkyl, phenyl, NR^8COR^9 , COR^9 , SO_2R^9 , $OCOR^9$, $NR^8SO_2R^9$ or $NR^8CO_2R^8$;

R^2 and R^3 are independently (1) hydrogen, (2) C_1-C_{10} alkyl or (3) C_1-C_{10} alkyl with 1 to 4 substituents selected from hydroxy, C_1-C_{10} alkoxy, or halogen;

X is (1) $-\text{CH}_2-$, (2) $-\text{CH}_2-\text{CH}_2-$, (3) $-\text{CH}=\text{CH}-$ or (4) $-\text{CH}_2\text{O}-$;

R^4 and R^5 are independently (1) hydrogen, (2) $\text{C}_1\text{-C}_{10}$ alkyl, (3) halogen, (4) NHR^8 , (5) OR^8 , (6) SO_2R^9 or (7) NHSO_2R^9 ;

R^6 is (1) hydrogen or (2) $\text{C}_1\text{-C}_{10}$ alkyl;

R^7 is $\text{Z}-(\text{R}^{1a})_n$;

R^{1a} is (1) R^1 , (2) $\text{C}_3\text{-C}_8$ cycloalkyl, (3) phenyl optionally substituted with up to 4 groups independently selected from R^8 , NR^8R^8 , OR^8 , SR^8 or halogen, or (4) 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, optionally substituted with up to four groups independently selected from oxo, R^8 , NR^8R^8 , OR^8 , SR^8 , or halogen;

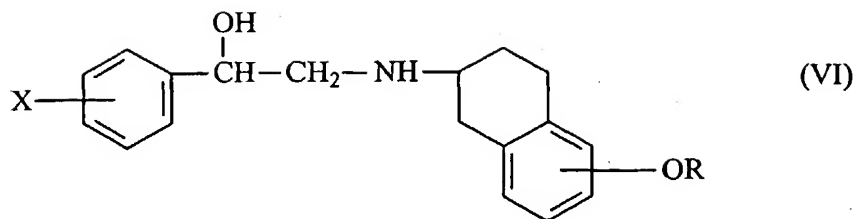
Z is (1) phenyl, (2) naphthyl, (3) or a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, (4) a benzene ring fused to a $\text{C}_3\text{-C}_8$ cycloalkyl ring, (5) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, (6) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, or (7) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen fused to a $\text{C}_3\text{-C}_8$ cycloalkyl ring;

R^8 is (1) hydrogen, (2) $\text{C}_1\text{-C}_{10}$ alkyl, (3) $\text{C}_3\text{-C}_8$ cycloalkyl, (4) Z optionally having 1 to 4 substituents selected from halogen, nitro, oxo, $\text{NR}^{10}\text{R}^{10}$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_1\text{-C}_{10}$ alkylthio, and $\text{C}_1\text{-C}_{10}$ alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO_2H , $\text{CO}_2\text{-C}_1\text{-C}_{10}$ alkyl, $\text{SO}_2\text{-C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, or Z optionally substituted by from 1 to 3 halogen, $\text{C}_1\text{-C}_{10}$ alkyl or $\text{C}_1\text{-C}_{10}$ alkoxy, or (5) $\text{C}_1\text{-C}_{10}$ alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO_2H , $\text{CO}_2\text{-C}_1\text{-C}_{10}$ alkyl, $\text{SO}_2\text{-C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_1\text{-C}_{10}$ alkyl, or Z optionally substituted by from 1 to 4 halogen, $\text{C}_1\text{-C}_{10}$ alkyl or $\text{C}_1\text{-C}_{10}$ alkoxy;

R^9 is (1) R^8 or (2) NR^8R^8 ; and

R^{10} is (1) $\text{C}_1\text{-C}_{10}$ alkyl, or (2) two R^{10} groups together with the N to which they are attached forming a 5 or 6-membered ring optionally substituted with $\text{C}_1\text{-C}_{10}$ alkyl;

(c) a compound of formula (VI) is:

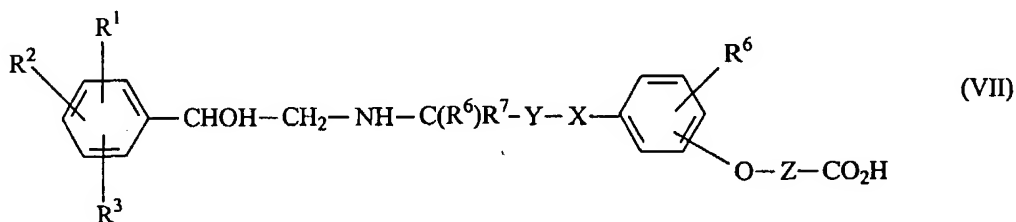


wherein

X is hydrogen, halogen, trifluoromethyl or lower alkyl, and

R is hydrogen; lower alkyl which may have a suitable substituent selected from the group consisting of cyclo(C₃-C₇)alkyl, hydroxy, lower alkoxy, carboxy and lower alkoxycarbonyl; cyclo(C₃-C₇)alkyl or lower alkanoyl;

(d) a compound of formula (VII) is represented by the following general formula:



wherein

R¹ is a hydrogen, fluorine, chlorine or bromine atom or a hydroxyl, hydroxymethyl, methyl, methoxyl, amino, formamido, acetamido, methylsulphonylamido, nitro, benzyloxy, methylsulphonylmethyl, ureido, trifluoromethyl or p-methoxybenzylamino group;

R² is a hydrogen, fluorine, chlorine or bromine atom or a hydroxyl group;

R³ is a hydrogen, chlorine or bromine atom or a hydroxyl group,

R⁴ is a hydrogen atom or a methyl group;

R⁵ is a hydrogen atom or a methyl group;

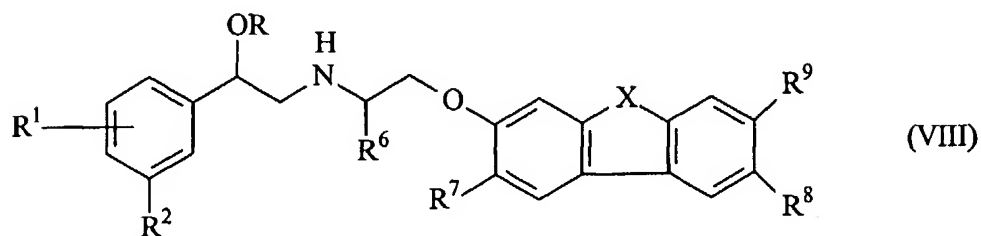
R⁶ is a hydrogen, fluorine or chlorine atom or a methyl, methoxyl or hydroxy group;

X is an oxygen atom or a bond;

Y is an alkylene group of up to 6 carbon atoms or a bond; and

Z is an alkylene, alkenylene or alkynylene group of up to 10 carbon atoms; and

(e) a compound of formula (VIII) is represented by the following general formula:



wherein

R is hydrogen or methyl,

R¹ is hydrogen, halogen, hydroxy, benzyloxy, amino or hydroxymethyl,

R² is hydrogen, hydroxymethyl, -NHR³, -SO₂NR⁴R^{4'} or nitro,

R³ is hydrogen, methyl, -SO₂R⁵, formyl or -CONHR⁶,

R⁴ and R^{4'} are independently hydrogen, lower alkyl or benzyl,

R⁵ is lower alkyl, benzyl or -NR⁴R^{4'},

R⁶ is hydrogen or lower alkyl,

R⁶ is hydrogen or lower alkyl,

R⁹ is hydrogen, amino, acetylamino or hydroxy, and

X is N, O, S or methylene;

provided that when X is N, O or S,

then R⁹ is hydrogen, either R⁷ or R⁸ is hydrogen, and the other is hydrogen, amino, acetylamino or hydroxy; and

provided that when X is methylene,

then both R⁷ and R⁸ are hydrogen.

--17. (Twice amended) A method for the prophylactic and/or the therapeutic treatment of pollakiuria or urinary incontinence comprising administering to a subject in need thereof an effective amount of

[the compound as defined in Claim 10 or a pharmaceutically acceptable salt thereof]

a compound, which is a β_2 adrenergic receptor agonist, having a general formula selected from the group consisting of formula (IV), (V), (VI), (VII) and (VIII).

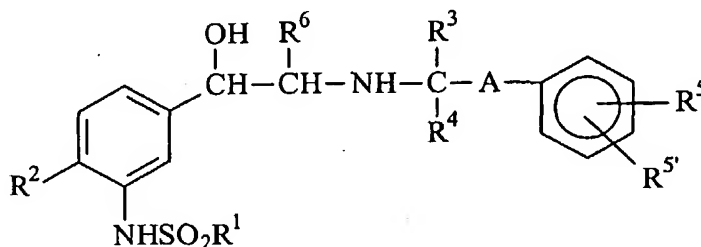
or a salt or prodrug thereof, or for the compound of formula (VII) an ester or amide

thereof:

wherein

(a) a compound of formula (IV) is represented by the following general formula:

wherein



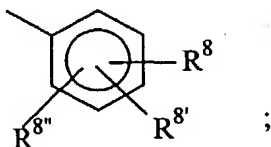
(IV)

R^1 is lower alkyl, aryl or arylalkyl;

R^2 is hydrogen, hydroxy, alkoxy, $-\text{CH}_2\text{OH}$, cyano, $-\text{C}(\text{O})\text{OR}^7$, $-\text{CO}_2\text{H}$, $-\text{CONH}_2$,

tetrazole, $-\text{CH}_2\text{NH}_2$ or halogen;

R^3 is hydrogen, alkyl, heterocycle or



R^4 is hydrogen, alkyl or B;

R^5 , $\text{R}^{5'}$, R^8 , $\text{R}^{8'}$ and $\text{R}^{8''}$ are independently hydrogen, alkoxy, lower alkyl, halogen, $-\text{OH}$, $-\text{CN}$, $-(\text{CH}_2)_n\text{NR}^6\text{COR}^7$, $-\text{CON}(\text{R}^6)\text{R}^6$, $-\text{CON}(\text{R}^6)\text{OR}^6$, $-\text{CO}_2\text{R}^6$, $-\text{SR}^7$, $-\text{SOR}^7$, $-\text{SO}_2\text{R}^7$, $-\text{N}(\text{R}^6)\text{SO}_2\text{R}^1$, $-\text{N}(\text{R}^6)\text{R}^6$, $-\text{NR}^6\text{COR}^7$, $-\text{OCH}_2\text{CON}(\text{R}^6)\text{R}^6$, $-\text{OCH}_2\text{CO}_2\text{R}^7$ or aryl; or

R^5 and $\text{R}^{5'}$ or R^8 and $\text{R}^{8'}$ may together with the carbon atoms to which they are attached form an aryl or heterocycle;

R^6 and $\text{R}^{6'}$ are independently hydrogen or lower alkyl; and

R^7 is lower alkyl;

R^9 and $\text{R}^{9'}$ are independently hydrogen, lower alkyl, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; or

R^9 and $\text{R}^{9'}$ may together with the nitrogen atom to which they are attached form a heterocycle;

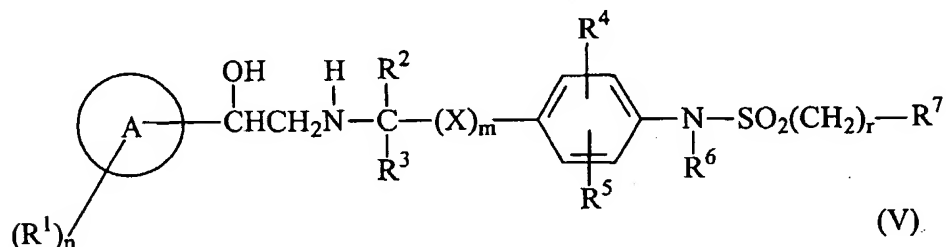
A is a bond, $-(\text{CH}_2)_n-$ or $-\text{CH}(\text{B})-$, wherein n is an integer of 1, 2 or 3 and

B is -CN, -CON(R⁹)R^{9'}- or -CO₂R⁷;

with the proviso that when A is a bond or -(CH₂)_n- and R³ is hydrogen or unsubstituted alkyl, then R⁴ is B or substituted alkyl;

(b) a compound of formula (V) is represented by the following general formula:

wherein



n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is pyridinyl;

R¹ is (1) hydroxy, (2) oxo, (3) halogen, (4) cyano, (5) NR⁸R⁸, (6) SR⁸, (7) trifluoromethyl, (8) C₁-C₁₀ alkyl, (9) OR⁸, (10) SO₂R⁹, (11) OCOR⁹, (12) NR⁸COR⁹, (13) COR⁹, (14) NR⁸SO₂R⁹, (15) NR⁸CO₂R⁸, or (16) C₁-C₁₀ alkyl substituted by hydroxy, halogen, cyano, NR⁸R⁸, SR⁸, trifluoromethyl, OR⁸, C₃-C₈ cycloalkyl, phenyl, NR⁸COR⁹, COR⁹, SO₂R⁹, OCOR⁹, NR⁸SO₂R⁹ or NR⁸CO₂R⁸;

R² and R³ are independently (1) hydrogen, (2) C₁-C₁₀ alkyl or (3) C₁-C₁₀ alkyl with 1 to 4 substituents selected from hydroxy, C₁-C₁₀ alkoxy, or halogen;

X is (1) -CH₂-, (2) -CH₂-CH₂-, (3) -CH=CH- or (4) -CH₂O-;

R⁴ and R⁵ are independently (1) hydrogen, (2) C₁-C₁₀ alkyl, (3) halogen, (4) NHR⁸, (5) OR⁸, (6) SO₂R⁹ or (7) NHSO₂R⁹;

R⁶ is (1) hydrogen or (2) C₁-C₁₀ alkyl;

R⁷ is Z-(R^{1a})_n;

R^{1a} is (1) R¹, (2) C₃-C₈ cycloalkyl, (3) phenyl optionally substituted with up to 4 groups independently selected from R⁸, NR⁸R⁸, OR⁸, SR⁸ or halogen, or (4) 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, optionally substituted with up to four groups independently selected from oxo, R⁸, NR⁸R⁸, OR⁸, SR⁸, or halogen;

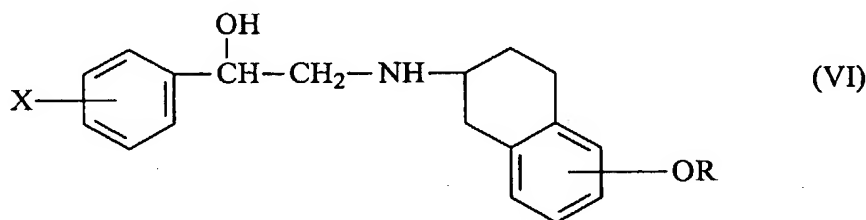
Z is (1) phenyl, (2) naphthyl, (3) or a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, (4) a benzene ring fused to a C₃-C₈ cycloalkyl ring, (5) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, (6) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, or (7) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen fused to a C₃-C₈ cycloalkyl ring;

R⁸ is (1) hydrogen, (2) C₁-C₁₀alkyl, (3) C₃-C₈ cycloalkyl, (4) Z optionally having 1 to 4 substituents selected from halogen, nitro, oxo, NR¹⁰R¹⁰, C₁-C₁₀alkyl, C₁-C₁₀alkoxy, C₁-C₁₀alkylthio, and C₁-C₁₀alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO₂H, CO₂-C₁-C₁₀alkyl, SO₂-C₁-C₁₀alkyl, C₃-C₈ cycloalkyl, C₁-C₁₀alkoxy, or Z optionally substituted by from 1 to 3 halogen, C₁-C₁₀alkyl or C₁-C₁₀alkoxy, or (5) C₁-C₁₀alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO₂H, CO₂-C₁-C₁₀alkyl, SO₂-C₁-C₁₀alkyl, C₃-C₈ cycloalkyl, C₁-C₁₀alkoxy, C₁-C₁₀alkyl, or Z optionally substituted by from 1 to 4 halogen, C₁-C₁₀alkyl or C₁-C₁₀alkoxy;

R⁹ is (1) R⁸ or (2) NR⁸R⁸; and

R¹⁰ is (1) C₁-C₁₀alkyl, or (2) two R¹⁰ groups together with the N to which they are attached forming a 5 or 6-membered ring optionally substituted with C₁-C₁₀alkyl;

(c) a compound of formula (VI) is:

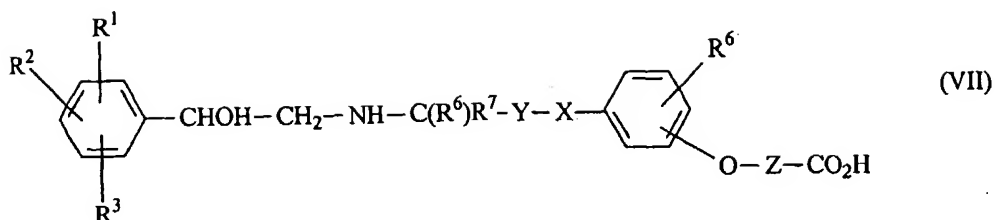


wherein

X is hydrogen, halogen, trifluoromethyl or lower alkyl, and

R is hydrogen; lower alkyl which may have a suitable substituent selected from the group consisting of cyclo(C₃-C₇)alkyl, hydroxy, lower alkoxy, carboxy and lower alkoxycarbonyl; cyclo(C₃-C₇)alkyl or lower alkanoyl;

(d) a compound of formula (VII) is represented by the following general formula:



wherein

R¹ is a hydrogen, fluorine, chlorine or bromine atom or a hydroxyl, hydroxymethyl, methyl, methoxyl, amino, formamido, acetamido, methylsulphonylamido, nitro, benzyloxy, methylsulphonylmethyl, ureido, trifluoromethyl or p-methoxybenzylamino group;

R² is a hydrogen, fluorine, chlorine or bromine atom or a hydroxyl group;

R³ is a hydrogen, chlorine or bromine atom or a hydroxyl group;

R⁴ is a hydrogen atom or a methyl group;

R⁵ is a hydrogen atom or a methyl group;

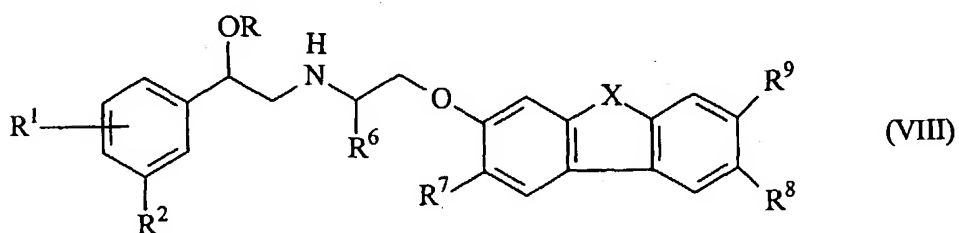
R⁶ is a hydrogen, fluorine or chlorine atom or a methyl, methoxyl or hydroxy group;

X is an oxygen atom or a bond;

Y is an alkylene group of up to 6 carbon atoms or a bond; and

Z is an alkylene, alkenylene or alkynylene group of up to 10 carbon atoms; and

(e) a compound of formula (VIII) is represented by the following general formula:



wherein

R is hydrogen or methyl.

R¹ is hydrogen, halogen, hydroxy, benzyloxy, amino or hydroxymethyl.

R² is hydrogen, hydroxymethyl, -NHR³, -SO₂NR⁴R⁴ or nitro.

R³ is hydrogen, methyl, -SO₂R⁵, formyl or -CONHR⁶.

R⁴ and R⁴ are independently hydrogen, lower alkyl or benzyl.

R⁵ is lower alkyl, benzyl or -NR⁴R⁴.

R⁶ is hydrogen or lower alkyl.

R⁶ is hydrogen or lower alkyl.

R⁹ is hydrogen, amino, acetylamino or hydroxy, and

X is N, O, S or methylene;

provided that when X is N, O or S,

then R⁹ is hydrogen, either R⁷ or R⁸ is hydrogen, and the other is hydrogen, amino, acetylamino or hydroxy; and

provided that when X is methylene,

then both R⁷ and R⁸ are hydrogen.

18. (Twice amended) A method for the prophylactic and/or the therapeutic treatment of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis, overflow incontinence, passive incontinence, reflex incontinence, urge incontinence, urinary stress incontinence comprising administering to a subject in need thereof an effective amount of a compound,

[as defined in Claim 10 or a pharmaceutically acceptable salt thereof]

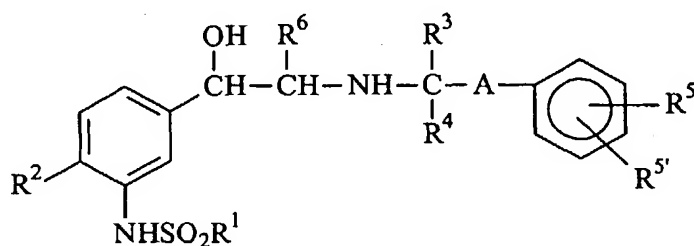
which is a β_1 adrenergic receptor agonist, having a general formula selected from the group consisting of formula (IV), (V), (VI), (VII) and (VIII).

or a salt or prodrug thereof, or for the compound of formula (VII) an ester or amide thereof;

wherein

(a) a compound of formula (IV) is represented by the following general formula:

wherein



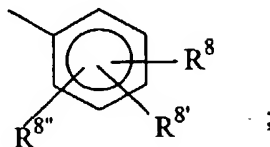
(IV)

R¹ is lower alkyl, aryl or arylalkyl;

R² is hydrogen, hydroxy, alkoxy, -CH₂OH, cyano, -C(O)OR⁷, -CO₂H, -CONH₂,

tetrazole, -CH₂NH₂ or halogen;

R³ is hydrogen, alkyl, heterocycle or



R⁴ is hydrogen, alkyl or B;

R⁵, R^{5'}, R⁸, R^{8'} and R^{8''} are independently hydrogen, alkoxy, lower alkyl, halogen, -OH, -CN, -(CH₂)_nNR⁶COR⁷, -CON(R⁶)R^{6'}, -CON(R⁶)OR^{6'}, -CO₂R⁶, -SR⁷, -SOR⁷, -SO₂R⁷, -N(R⁶)SO₂R¹, -N(R⁶)R^{6'}, -NR⁶COR⁷, -OCH₂CON(R⁶)R^{6'}, -OCH₂CO₂R⁷ or aryl; or

R⁵ and R^{5'} or R⁸ and R^{8'} may together with the carbon atoms to which they are attached form an aryl or heterocycle;

R⁶ and R^{6'} are independently hydrogen or lower alkyl; and

R⁷ is lower alkyl;

R⁹ and R^{9'} are independently hydrogen, lower alkyl, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; or

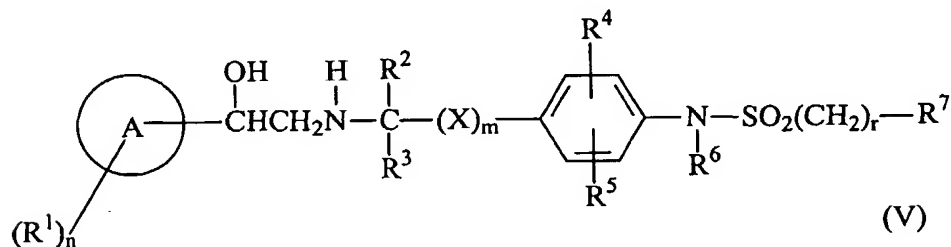
R⁹ and R^{9'} may together with the nitrogen atom to which they are attached form a heterocycle;

A is a bond, -(CH₂)_n- or -CH(B)-, wherein n is an integer of 1, 2 or 3 and B is -CN, -CON(R⁹)R^{9'}- or -CO₂R⁷;

with the proviso that when A is a bond or -(CH₂)_n- and R³ is hydrogen or unsubstituted alkyl, then R⁴ is B or substituted alkyl;

(b) a compound of formula (V) is represented by the following general formula:

wherein



n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is pyridinyl;

R¹ is (1) hydroxy, (2) oxo, (3) halogen, (4) cyano, (5) NR⁸R⁸, (6) SR⁸, (7) trifluoromethyl, (8) C₁-C₁₀ alkyl, (9) OR⁸, (10) SO₂R⁹, (11) OCOR⁹, (12) NR⁸COR⁹, (13) COR⁹, (14) NR⁸SO₂R⁹, (15) NR⁸CO₂R⁸, or (16) C₁-C₁₀ alkyl substituted by hydroxy, halogen, cyano, NR⁸R⁸, SR⁸, trifluoromethyl, OR⁸, C₃-C₈ cycloalkyl, phenyl, NR⁸COR⁹, COR⁹, SO₂R⁹, OCOR⁹, NR⁸SO₂R⁹ or NR⁸CO₂R⁸.

R² and R³ are independently (1) hydrogen, (2) C₁-C₁₀ alkyl or (3) C₁-C₁₀ alkyl with 1 to 4 substituents selected from hydroxy, C₁-C₁₀ alkoxy, or halogen;

X is (1) -CH₂CH₂-, (2) -CH₂-, (3) -CH=CH- or (4) -CH₂O-;

R⁴ and R⁵ are independently (1) hydrogen, (2) C₁-C₁₀ alkyl, (3) halogen, (4) NHR⁸, (5) OR⁸, (6) SO₂R⁹ or (7) NHSO₂R⁹;

R⁶ is (1) hydrogen or (2) C₁-C₁₀ alkyl;

R⁷ is Z-(R^{1a})_n;

R^{1a} is (1) R¹, (2) C₃-C₈ cycloalkyl, (3) phenyl optionally substituted with up to 4 groups independently selected from R⁸, NR⁸R⁸, OR⁸, SR⁸ or halogen, or (4) 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, optionally substituted with up to four groups independently selected from oxo, R⁸, NR⁸R⁸, OR⁸, SR⁸, or halogen;

Z is (1) phenyl, (2) naphthyl, (3) or a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, (4) a benzene ring fused to a C₃-C₈ cycloalkyl ring, (5) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, (6) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, or (7) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen fused to a C₃-C₈ cycloalkyl ring;

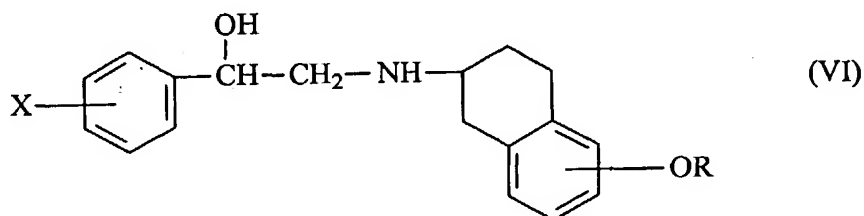
R⁸ is (1) hydrogen, (2) C₁-C₁₀ alkyl, (3) C₃-C₈ cycloalkyl, (4) Z optionally having 1 to 4 substituents selected from halogen, nitro, oxo, NR¹⁰R¹⁰, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylthio, and C₁-C₁₀ alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO₂H, CO₂-C₁-C₁₀ alkyl, SO₂-C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₁-C₁₀ alkoxy, or Z optionally substituted by from 1 to 3 halogen, C₁-C₁₀ alkyl or C₁-C₁₀ alkoxy, or (5) C₁-C₁₀ alkyl having 1

to 4 substituents selected from hydroxy, halogen, CO_2H , $\text{CO}_2\text{-C}_1\text{-C}_{10}\text{ alkyl}$, $\text{SO}_2\text{-C}_1\text{-C}_{10}\text{ alkyl}$, $\text{C}_3\text{-C}_8\text{ cycloalkyl}$, $\text{C}_1\text{-C}_{10}\text{ alkoxy}$, $\text{C}_1\text{-C}_{10}\text{ alkyl}$, or Z optionally substituted by from 1 to 4 halogen, $\text{C}_1\text{-C}_{10}\text{ alkyl}$ or $\text{C}_1\text{-C}_{10}\text{ alkoxy}$;

R^9 is (1) R^8 or (2) NR^8R^8 ; and

R^{10} is (1) $\text{C}_1\text{-C}_{10}\text{ alkyl}$, or (2) two R^{10} groups together with the N to which they are attached forming a 5 or 6-membered ring optionally substituted with $\text{C}_1\text{-C}_{10}\text{ alkyl}$;

(c) a compound of formula (VI) is:

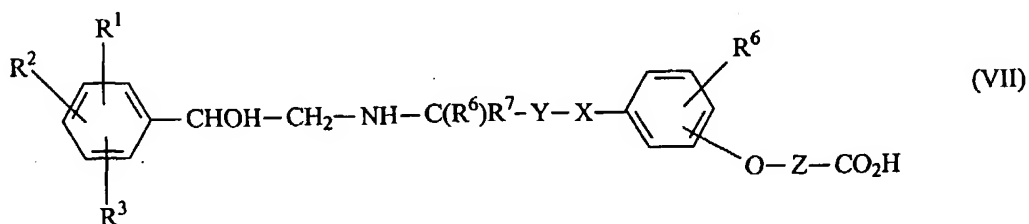


wherein

X is hydrogen, halogen, trifluoromethyl or lower alkyl, and

R is hydrogen; lower alkyl which may have a suitable substituent selected from the group consisting of cyclo($\text{C}_3\text{-C}_7$)alkyl, hydroxy, lower alkoxy, carboxy and lower alkoxy carbonyl; cyclo($\text{C}_3\text{-C}_7$)alkyl or lower alkanoyl;

(d) a compound of formula (VII) is represented by the following general formula:



wherein

R^1 is a hydrogen, fluorine, chlorine or bromine atom or a hydroxyl, hydroxymethyl, methyl, methoxyl, amino, formamido, acetamido, methylsulphonylamido, nitro, benzyloxy, methylsulphonylmethyl, ureido, trifluoromethyl or p-methoxybenzylamino group;

R^2 is a hydrogen, fluorine, chlorine or bromine atom or a hydroxyl group;

R^3 is a hydrogen, chlorine or bromine atom or a hydroxyl group.

R⁴ is a hydrogen atom or a methyl group;

R⁵ is a hydrogen atom or a methyl group;

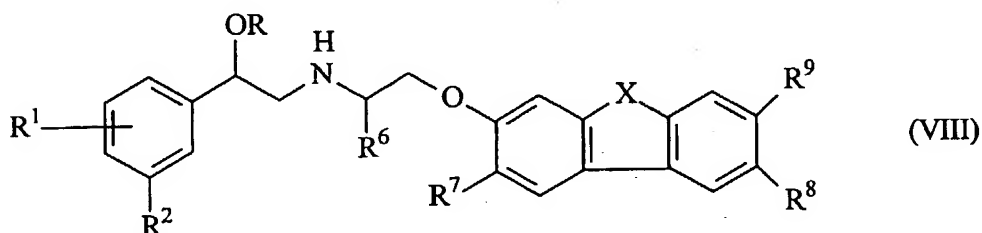
R⁶ is a hydrogen, fluorine or chlorine atom or a methyl, methoxyl or hydroxy group;

X is an oxygen atom or a bond;

Y is an alkylene group of up to 6 carbon atoms or a bond; and

Z is an alkylene, alkenylene or alkynylene group of up to 10 carbon atoms; and

(e) a compound of formula (VIII) is represented by the following general formula:



wherein

R is hydrogen or methyl.

R¹ is hydrogen, halogen, hydroxy, benzyloxy, amino or hydroxymethyl.

R² is hydrogen, hydroxymethyl, -NHR³, -SO₂NR⁴R⁴ or nitro.

R³ is hydrogen, methyl, -SO₂R⁵, formyl or -CONHR⁶.

R⁴ and R⁴ are independently hydrogen, lower alkyl or benzyl.

R⁵ is lower alkyl, benzyl or -NR⁴R⁴.

R⁶ is hydrogen or lower alkyl.

R⁶ is hydrogen or lower alkyl.

R⁹ is hydrogen, amino, acetylamino or hydroxy, and

X is N, O, S or methylene;

provided that when X is N, O or S,

then R⁹ is hydrogen, either R⁷ or R⁸ is hydrogen, and the other is hydrogen, amino,

acetylamino or hydroxy; and

provided that when X is methylene,

then both R⁷ and R⁸ are hydrogen.

--19. (Twice amended) A commercial package comprising:

[the compound as defined in Claim 10]